Available online at www.elixirpublishers.com (Elixir International Journal)

Applied Chemistry

Elixir Appl. Chem. 116C (2018) 50329-50332

ISSN: 2229-712X

Antibacterial Activity of 4-butanoyl-3-methyl-1-phenylpyrazol-5-one and its Manganese(II), Lanthanum(III), Zirconium(III), Vanadium(V) and Tungsten(VI) Complexes

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ARTICLE INFO

Article history:

Received: 19 February 2018;

Received in revised form:

20 March 2018;

Accepted: 31 March 2018;

Keywords

4-butanoyl-3-methyl-1-phenylpyrazol-5-one,

Metal Complexes,

Antibiotics,

Antibacterial activity.

ABSTRACT

The ligand, 4-butanoyl-3-methyl-1-phenylpyrazol-5-one (HBPy) and its complexes with Mn(II), La(III), Zr(III), V(V) and W(VI) were tested for antibacterial activity relative to streptomycin and penicillin antibiotics. The filter paper scraps diffusion method was used. The compounds were screened for their in vitro antibacterial activity against G(+) Staphylococcus aureus, G(+) Hay bacillus and G(-) Eschericha coli. It could be observed from the results that the antibacterial effect of the $Mn(BPy)_2.2H_2O$ and the $VO_2(BPy).HBPy$ complexes were similar to that of penicillin against the two G(+) strains. The other three complexes also had such antibacterial activity, but a little weaker than that of penicillin. The test data also indicated that streptomycin was intermediately effective against G(+) *Hay bacillus.* The five complexes at a concentration of 2 µg/disc, showed antibacterial activity against G(+) *Hay bacillus* comparable to that of streptomycin with a concentration of 10 µg/disc. The ligand and its complexes showed none or much weaker antibacterial activity compared to penicillin and streptomycin against G(-) *Eschericha coli.* It is therefore concluded that the metal complexes studied are potent against the Gram-positive bacteria studied; hence the compounds have great potentials in the exploration of new chemotherapy agents.

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1.0 INTRODUCTION

Pyrazol-5-one and its derivatives are widely used precursor to a variety of compounds, documented well for their numerous applications such as products and intermediates in analytical, agricultural, biological, and pharmaceutical chemistry, extractants in mineral processing (Bojan, Marijan & Slovenko, 2009; Jung, Watkins & Avery, 2002; Kimata e*t al.*, 2007; Ogwuegbu & Chileshe, 2000). Some of them also serve as important pharmaceutical agents including antipyrine and its congeners. With continuous evaluation for their pharmacological properties like analgesic (Gursov, Demiyarak, Capan, Erol & Vural, 2000), anti-inflammatory (Satyanarayana & Rao, 1995), antiarrhythmic, antifungal (Bekhit & Fahmy, 2003) potential antipyretic (Souza *et al.*, 2002), antinociceptive (Tabarelli *et al.*, 2004; Prokopp *et al.*, 2006) and antioxidant activities (Godoy *et al.*, 2004), the pyrazolone derivatives have still attracted medicinal chemists' interests. Recently, acylpyrazolones have been reported to have a multidrug resistance modulating activity (Kimata *et al.*, 2007). Benzoylpyrazolones, particularly, are potential antiprion agents (Chiba *et al.*, 1998). Synthesis, antimicrobial and antioxidant activities of some 5-pyrazolone based schiff bases derived from a condensation reaction of 4-acyl-5-pyrazolones with aromatic diamines have been reported by Parmara *et al* (2015).

The potential applications of pyrazolones in medicine as strong analgesic, antihistaminic, antipyretic, antibacterial and anti-fungal have been reported (Raman, Raja, Joseph and Ohaveeth, 2007; Sarbani, Jyoti and Nalla, 2008). Medicinal chemists have used pyrazolones extensively as scaffolds from which to design novel therapeutic agents (Brugel *et al.*, 2006).

Obviously, the potential applications of 4-acylpyrazolones in medicine, in the extraction and construction of ion-exchange resins for metal ions are the incentives behind the investigation of the interaction between these chelating agents and metal ions in solution (Marchetti, Pettinari & Pettinari, 2005).

However, the study of biological activities of this class of compounds and their metal complexes is largely restricted to studies on microorganisms. Few reports are available in the literature on the study of their antibacterial activities. With the increasing search for more antibacterial substances with fewer side effects, other than the conventional antibiotics for pollution abatement of microorganisms from effluents discharge, it is imperative to investigate the possibility of the use of 4-acylpyrazolone derivatives.

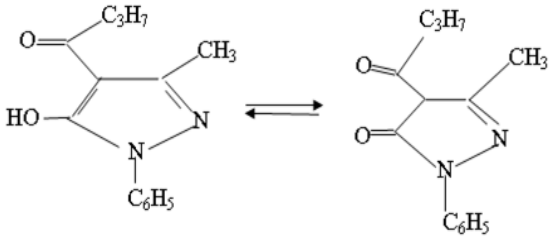

Figure 1: Structures of the keto-enol tautomeric forms of the 4-butanoyl-3-methyl-1-phenylpyrazol-5-one.

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In this paper, antibacterial activities of 4-butanoyl-3-methyl-1-phenylpyrazol-5-one and its manganese(II), lanthanum(III), zirconium(III), vanadium(V) and tungsten(VI) complexes relative to some familiar antibiotics was reported. The structures of the keto–enol tautomeric forms of the 4-butanoyl-3-methyl-1-phenylpyrazol-5-one (designated here as **HBPy)** are as shown in Figure 1.

In our previous work, the syntheses and characterization of the 4-butanoyl-3-methyl-1-phenylpyrazol-5-one and its Mn(II), Zr(III), La(III), V(V) and W(VI) complexes; the mode of interactions between the metals and the ligand in aqueous solution and the possible structures of the ligand and the complexes were reported (Ehirim, Elenwoke & Ogwuegbu, 2014). The present study was carried out to investigate the possible antibacterial activity of the synthesized ligand, 4-butanoyl-3-methyl-1-phenylpyrazol-5-one and its Mn(II), Zr(III), La(III), V(V) and W(VI) complexes relative to familiar antibiotics namely: penicillin and streptomycin.

2.0. EXPERIMENTAL

2.1. Reagents: Analytical grade reagents including 95 % ethanol and dimethylsulphoxide (DMSO), 4-butanoyl-3-methyl-1-phenylpyrazol-5-one and its Mn(II), Zr(III), La(III), V(V) and W(VI) complexes, distilled de-mineralized water, filter paper, streptomycin and penicillin.

2.2. Antibacterial activity tests

In-vitro antibacterial activity of the ligand and its complexes was studied by using the filter paper scraps diffusion method. The strains chosen included G(+) *Staphylococcus aureus*, G(+) *Hay bacillus*, and G(-) *Eschericha coli*. Small 6 mm diameter circular scraps of filter paper were prepared for the purpose of bacteriostatic slices. 2 mg of drug (the ligand and its metal complexes) was dissolved in 10 ml DMSO (1 %) to make concentrations of 0.2 mg/ml. The solution (0.2 ml) was poured into a small bottle containing ten paper slices and it was ensured that all the solution was blotted up. The bottle was covered by gauze, sterilized for 20 minutes under a steam pressure of 15 Ib/in^2, and then kept in an oven at 80 ^{o}C for subsequent testing (Qin-xi *et al.*, 2000).

Bacterial strains were inoculated into the medium plates with absorbent cotton, and three previously prepared bacteriostatic slices containing the same drug were put on a medium plate. One sample was inoculated in parallel on four medium plates. Finally, all plates were incubated at 35 ^{o}C in 5 % CO_2 for 24 hours and then examined. Streptomycin and penicillin were used as standard antibacterial drugs (control). Solvent was screened for its activity. The corrections in biological activity of the compound, due to solvent dimethylsulphoxide (DMSO) were also applied in the calculation.

At the end of incubation time, the diameters of the inhibition zones formed on the filter paper scraps were evaluated in millimeters. The measured inhibition zones of the study compounds were compared with those of the reference discs (Asegbeloyin *et al.*, 2014).

3.0. RESULTS AND DISCUSSION

The results of the analyses and their discussion are presented below.

3.1: Antibacterial activity of the ligand and its complexes.

The results of the antibacterial activity of the ligand and its complexes are presented in Table 1.

The susceptibility of a certain bacterial strain towards an antibacterial drug can be tested by measuring the bacteriostatic diameter (d). For penicillin with a concentration of 2.0 μg/disc, d >= 20 mm shows high sensitivity, 14 <= d< 20 mm indicates intermediate sensitivity, while 9<= d <= 13 shows slight sensitivity (Qui-xi *et al.*, 2000). From the results in Table 1, penicillin is highly effective against G(+) *Staphylococcus aureus* and *G(+) Hay bacillus*. It could be observed from the results that the antibacterial effect of the $Mn(BPy)_2.2H_2O$ and the $VO_2(BPy).HBPy$ complexes were similar to that of penicillin against the two G(+) strains. The other three complexes also had such antibacterial activity, but a little weaker than that of penicillin. For streptomycin with a concentration of 10 μg/disc, d>19, 14<d<= 18, and 12<d<= 13 indicate high, intermediate and slight sensitivities respectively. The test data indicated that streptomycin was intermediately effective against G(+) *Hay bacillus.* The five complexes at a concentration of 2 μg/disc, showed antibacterial activity against G(+) *Hay bacillus* comparable to that of streptomycin with a concentration of 10 μg/disc. Therefore, considering the concentrations, these complexes have considerably stronger antibacterial activity than that of streptomycin against G(+) *Hay bacillus*. The ligand and its complexes showed none or much weaker antibacterial activity compared to penicillin and streptomycin against G(-) *Eschericha coli*.

The observed results of the antimicrobial tests of the ligand and its complexes against the G(-) *E. coli* could be attributed to the inability of the compounds to permeate the protective outer membrane of the Gram negative bacteria to the extent of having antimicrobial effects. Similar observation had been made elsewhere (Asegbeloyin *et al*, 2014).

This is because Gram-negative bacteria are noted for the presence of protective lipopolysaccharide (LPS) in the outer membrane of their cell wall, which protects the sensitive inner membrane and the cell wall from drugs and dyes (Nikaido, 1994). This protective lipopolysaccharide is absent in Gram-positive bacteria. In order for these compounds to exert bacteriostatic or bactericidal actions, they must access intracellular targets (Poole, 2002). Therefore, in Gram-negative bacteria, these compounds must cross the outer membrane, a substantial permeability barrier and thus a major determinant of antimicrobial resistance in these bacteria (Todar, 2011). Finally, it is noteworthy that the antibacterial activities of the complexes were stronger than that of the ligand. The observed better antimicrobial action exhibited by the complexes may be ascribed to possible binding of the

Table 1. The antibacterial activity data of the ligand, its complexes and the standard drugs.

Drug on disc	Concentration (μg/disc)	Average value of bacteriostatic diameter (mm) G(+) Staphylococ aureus	G(+) Hay bacillus	G(-) E. coli
HBPy	2	12.5	11.0	0.0
$Mn(BPy)_2.2H_2O$	2	21.5	17.5	5.0
$La(BPy)_3.2H_2O$	2	16.5	13.5	3.0
$Zr(BPy)_3.2H_2O$	2	15.0	14.0	3.0
$VO_2(BPy).HBPy$	2	20.5	16.5	5.5
$WO_2(BPy)_2.H_2O$	2	15.5	14.0	4.0
Penicillin	2	23.0	20.0	16.5
Streptomycin	10	0.0	16.5	18.0

central metal ions in these complexes to the active centres of cell constituents of the bacteria studied, thereby preventing their activities.

4.0. CONCLUSION

The compounds exhibited better antibacterial activity against Gram-positive bacterial strains studied but did not show such antibacterial activity on the Gram-negative E. coli bacteria.

From the above analysis, it can be said that the activities of the complexes, especially $Mn(HBPy)_2.2H_2O$ and $VO_2(BPy).HBPy$ complexes against G(+) *Staphylococcus aureus* and G(+) *Hay bacillus* have great potentials in the exploration of new chemotherapy agents.

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